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Original Research Article

Significance of blood serum catalase activity and malondialdehyde level for survival prognosis of ovarian cancer patients

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ABSTRACT

Background and objective: Several markers were found to be potential prognostic factors in ovarian cancer. Among markers resembling systemic changes in the host's organism are markers of the oxidative stress. In this study we attempted to analyze the oxidant and antioxidant parameters of ovarian cancer patients.

Materials and methods: A total of 42 patients with newly diagnosed stages I–IV primary ovary cancer were examined. Level of malondialdehyde (MDA) and catalytic activity catalase (CAT) were determined spectrophotometrically.

Results: Significantly lower CAT (28.2 ± 15.5 vs. 36.1 ± 14.6 nmol/L/min, $P = 0.019$) activity and higher MDA levels (8.7 ± 3.0 vs. 6.7 ± 2.7 nmol/L, $P = 0.002$) were observed in cancer patients compared with healthy volunteers. Both variables were not confirmed as prognostic factors according to Kaplan–Meier survival estimates.

Conclusions: MDA and CAT demonstrate oxidative stress in cancer patients: CAT activity was significantly lower and MDA levels higher in cancer patients compared to healthy controls. These variables were not confirmed to be prognostic factors in ovarian cancer, possibly due to small size of the study group.

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1. Introduction

Ovarian cancer is the second most common gynecologic oncologic disease in the world and third in developing countries. The worldwide incidence rate was estimated to be 6.1 per 100,000 women with mortality rates reaching 3.8 per 100,000 women [1]. Recently reported 5-year European mean survival rate was 37.6% [2]. The survival highly depends on the TNM stage of the disease. Patients with stage I of the diseases present with a favorable 89%–92% 5-year survival rate, while in patients with stage IV cancer it drops to 12%–18% [3]. Although the new chemotherapeutic agents prolonged the survival of ovarian cancer patients it still remains relatively short. This is due to the fact that most of the cases are diagnosed at late stages of the disease, when radical treatment is no longer possible. Nonspecific symptoms, insufficiently sensitive and specific diagnostic tools all contribute to this delay [4].

Therefore much effort has been made in search of biomarkers that would be of screening, prognostic and predictive value for patients with ovarian cancer. Unfortunately despite arduous research such markers are still to be found and the search for them remains a high priority [5]. Potential markers include substances that are produced by the cancer itself (such as CAE, CA-125), many of which are currently used in medical practice. Recent studies have also identified a specific profile of tumor vascular markers (TVM) [6]. Some of them were confirmed as potential screening, prognostic and predictive markers [7,8].

Another group of tumor markers is comprised of indicators of organism systemic response to the tumor. Among these are the antioxidant/oxidative parameters of the organism. Measurements of various components of antioxidant system have proven themselves to be valuable prognostic factors for patients with breast, gastric and oropharyngeal cancer [9–11]. However it is still unclear which components should be evaluated and what is the exact meaning of their fluctuations in cancer patients [12]. The activity of antioxidant components in particular is difficult to interpret, since it has been found to both rise and diminish in response to cancer [13–17].

Many studies have distinguished malondialdehyde (MDA) concentration that represents lipid peroxidation and catalase (CAT) activity, a crucial component of the antioxidant system [14]. Although their significance has been confirmed in many other cancers, up till now there is no unanimous opinion about their significance in patients with gynecological cancer.

The aim of the present study was to estimate if MDA level and CAT activity in blood serum of ovarian cancer patients are different from those of healthy women and can these variables be considered important for prognosis of ovarian cancer patient survival.

2. Materials and methods

2.1. Study group

A total of 42 patients with newly diagnosed primary ovary cancer at the Institute of Oncology, Vilnius University (Vilnius, Lithuania), were involved in the study group. The age of the patients varied from 22 to 67 years with the mean age being 49.6 ± 8.22 years. Staging was assessed according TNM classification. Out of 42 patients of ovarian carcinoma, 4.8% (two patients) had TNM stage I disease, 9.5% (four patients) stage II, 28.6% (12 patients) stage III and 57.1% (24 patients) had TNM stage IV disease.

2.2. Control group

The group included 42 healthy volunteers. They were matched by age (±1 year).

2.3. Analysis of MDA level and CAT activity

Level of lipid peroxidation product MDA (nmol/ml) and catalytic activity of enzyme CAT (nmol/l/min) were determined spectrophotometrically. MDA was tested by thiobarbituric acid (TBA) assay based on the release of color complex due to TBA reaction with MDA as described [15]. CAT activity was defined by the assay based on the rate of a hydrogen peroxide/ammonium molybdate complex formation according to Ref. [16].

2.4. Statistical analysis

Descriptive statistics were used to summarize study data. Results were expressed as mean ± SD. Statistical comparisons between groups were performed by Student t test. Survival was estimated by the Kaplan–Meier method. The statistical difference between the survival curves was determined using the log-rank test. A P value of <0.05 was considered statistically significant. For survival comparison, patients were divided by median age, and median levels of CAT and MDA level in cancer patients group. Statistical analysis was performed using Stata Statistical Software version 11.0 (StataCorp, 2009. Stata Statistical Software: Release 11.0, College Station, TX, USA).

3. Results

Blood serum samples from 42 newly diagnosed ovarian cancer patients and healthy volunteers have been analyzed, MDA level and CAT activity have been measured.

Cancer patients showed significantly lower CAT activity and significantly higher MDA levels compared to a control group of healthy women (28.2 ± 15.5 vs. 36.1 ± 14.6 nmol/L/min, $P = 0.019$ and 8.7 ± 3.0 vs. 6.7 ± 2.7 nmol/L, $P = 0.002$, respectively) (Table 1). Thus we have observed a depression in the antioxidant system and an increase in lipid peroxidation resembling oxidative stress in ovarian cancer patients.

Table 1 – Comparison of malondialdehyde (MDA) levels and catalase (CAT) activity in study and control groups.

Parameter	Control ($N = 42$)	Cases ($N = 42$)	P^*
MDA	6.73 ± 2.66	8.7 ± 2.99	0.002
CAT	36.10 ± 14.60	28.23 ± 15.55	0.019

* t test.

Table 2 – Comparison of malondialdehyde (MDA) levels and catalase (CAT) activity in different stages (TNM) of ovarian cancer patients.

Parameter	Stage I or II (N = 6)	Stage III (N = 12)	Stage IV (N = 24)	P
MDA	9.57 ± 4.09	7.73 ± 2.45	8.98 ± 2.94	0.6
CAT	39.50 ± 26.67	28.22 ± 10.32	25.43 ± 13.57	0.7

CAT activity was somewhat higher in patients with stage I–II cancer (39.50 nmol/L/min) than in stages III (28.2 nmol/L/min) and IV (25.4 nmol/L/min) (Table 2). However CAT activity was significantly different only between group consisting of stages I–II and group of stage IV ($P = 0.07$). For MDA levels no significant differences by stage of the disease were observed.

In survival analysis the only significant predictor was the stage of the disease ($P = 0.029$). No differences in overall survival was found between study subgroups defined by median level of CAT ($P = 0.7$) and MDA ($P = 0.6$) (Figure). No differences in survival were observed between the two age groups ($P = 0.18$).

4. Discussion

As we have noted, biomarkers of ovarian cancer are still lucrative, yet elusive means for screening and improving the outcome of ovarian cancer patients. In this study we assessed the levels of MDA and CAT in healthy controls and ovary cancer patients and compared their levels at different TNM stages of this disease. This was done to confirm the hypothesis that there is an imbalance between the level of MDA and the activity of CAT in cancer patients and might be one of the prognostic factors for survival of cancer patients. Significant differences in CAT activity and MDA concentrations were found between ovarian cancer patients and healthy controls. According to Kaplan–Meier survival estimates both variables were not confirmed as significant biomarkers for prognosis of survival of ovarian cancer patients. However this might be due to small sample sizes.

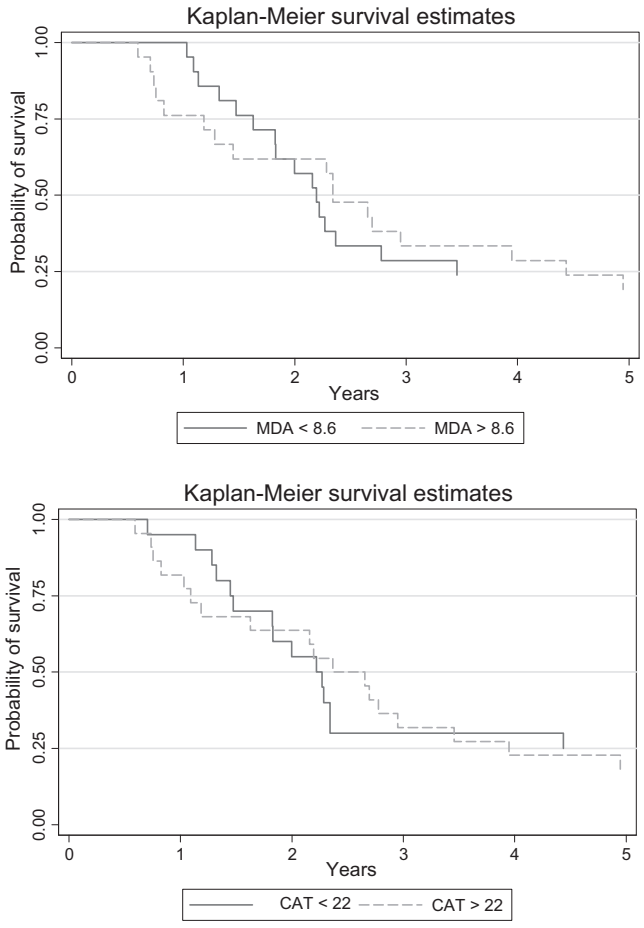

Figure – Kaplan–Meier curves of overall survival according to malondialdehyde (MDA) levels and catalase (CAT) activity.

Oxidative stress resembled by an increase in MDA and decrease in antioxidant parameters was also demonstrated in gastric, oropharyngeal, renal, breast and lung cancer and colorectal adenomas [10,18–20]. It was proven that in these cancer locations MDA levels are significantly higher and antioxidant parameters, such as CAT activity, lower compared to healthy controls.

Patients with colorectal adenomas have been found to have higher MDA levels as well as patients with malignant disease. There is also evidence of increase in plasma MDA in the presence of risk factors of colorectal carcinoma, such as high alcohol, saturated fat and meat intake. Meanwhile high fiber intake was found to be reversely proportionate to MDA level [19].

Similar increase in MDA has been observed in patients with gastric cancer compared to healthy control group. Additionally oxidative stress was resembled by an increase in reactive nitrogen species. This increase of oxidative stress was also found to be proportionate to the stage of the disease [10].

Oropharyngeal cancer patients have been found to have increased MDA levels compared to healthy controls. Test subjects with precancerous lesions also had higher MDA levels, which were however significantly lower than those in cancer patients [20]. Further studies showed that there is a correlation between the extent of primary tumor and MDA levels. Moreover higher MDA concentration was found to be associated with poor survival when measured before treatment and with a higher recurrence rate when assessed after surgery [11]. MDA was also established to be higher in the smokers group vs. nonsmokers' group [21].

It has been found that lung cancer patients have significantly higher MDA levels than healthy controls [21]. One study compared pre-treatment levels and post-treatment levels after three and six cycles of cisplatin + etoposide of lipid oxidation products (LOP), nitric oxide (NO), glutathione (GSH) and SOD activity. It has found that pre-treatment oxidation markers (LOP and NO) were lower and antioxidant markers (GSH and SOD) were higher when compared with results after the treatment. This indicates an overall increase in oxidative stress after chemotherapy. However LOP and NO levels were

lower and GSH and SOD activity higher in responders when compared with nonresponders. This may be attributed to the decrease of proliferation associated oxidative stress caused by cancer in responders, while the chemotherapy induced oxidative stress may be similar in both groups [21].

There is evidence of oxidative stress in breast cancer patients. It has been found that in patients with benign and malignant breast tumors MDA, NO levels are higher and CAT activity is lower than in the control group. Activity of several other antioxidant enzymes such as glutathione peroxidase and CuZn-superoxide dismutase were lower in blood plasma of patients with malignant disease [22]. However one study has showed that in patients with advanced breast cancer although NO levels are increased, MDA levels are lower when compared to a control group [23].

One of our studies analyzed IL-18 and MDA levels in patients with renal cell carcinoma before and after surgical treatment. It determined that IL-18 (an inflammatory mediator) was significantly higher after surgery if MDA was higher. Further analysis according to gender revealed that in the male group IL-18 concentration was higher and MDA levels were lower after surgery. Meanwhile in female group although IL-18 levels were also higher, MDA levels were not significantly different and CAT activity was higher. Finally SOD activity was found to be higher after surgery in both groups [24].

In this study we have demonstrated a depression in the antioxidative system and an increase in lipid peroxidation resembling oxidative stress in ovarian cancer patients. Previous studies report increased levels of MDA in breast cancer patients compared to healthy controls [15]. An elevated concentration of MDA has also been noted in the malignant tissue when compared to normal tissue samples from healthy controls [16]. Furthermore there was shown a trend toward higher MDA concentration in malignant tissue as the TNM stage increases [17]. Thus it has been proven that oxidative stress is present not only in cancerous cells, but in the whole organism affected by the tumor.

5. Conclusions

In conclusion, we established increased levels of lipid peroxidation and decreased capabilities of antioxidant system in patients with ovarian cancer compared to healthy volunteers. MDA level and CAT activity were not confirmed as prognostic markers for ovarian cancer patient survival in this study group.

Conflict of interest

The authors state no conflict of interest.

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